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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/611,440	BERINSTEIN ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *36,38 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 4-6, 9-11, 14-16, 19-21, 24-26, 29-31, 34, 35, 37, 40-44, 47-49, 52-54, 57-59 and 62-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,4-6,9-11,14-16,19-21,24-26,29-31,34-44,47-49,52-54,57-59 and 62-66.

DETAILED ACTION

Claims 2, 3, 7, 8, 12, 13, 17, 18, 22, 23, 27, 28, 32, 33, 45, 46, 50, 51, 55, 56, 60, 61 have been canceled. Claims 1, 4-6, 9-11, 14-16, 19-21, 24-26, 29-31, 34-44, 47-49, 52-54, 57-59 and 62-66 are pending. Claims 36, 38 and 39, drawn to non-elected inventions, remain withdrawn from consideration. Claims 1, 4-6, 9-11, 14-16, 19-21, 24-26, 29-31, 34, 35, 37, 40-44, 47-49, 52-54, 57-59 and 62-66 are under consideration.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34 and 35 are drawn to products and are dependent on claim 31 which is a method claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-6, 9-11, 14-16, 19-21, 24-26, 29-31, 34, 35, 37, 40-44, 47-49, 52-54, 57-59 and 62-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability

in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A)As drawn to a method of eliciting or enhancing an immune response against a tumor antigens by administering by administering expression vectors encoding immunoreactive fragments

Claims 1, 4-6, 9-11, 14-16, 19-21, 24-26, 29, 30, 34, 35, 40-44, 47-49, 52-54, 57-59, 62- and 63 are drawn to the expression vectors or compositions comprising the nucleic acids of SEQ ID NO:1 or nucleic acids encoding immunogenic fragments of SEQ ID NO:1, or comprising a nucleic acid encoding SEQ ID NO:2 or immunogenic fragments of SEQ ID NO:2 . Claims 64-66 are drawn to pharmaceutical composition comprising nucleic acid expression vectors. Claims 31-35 and 37 are drawn in part to a method of inducing an immune response against a tumor-associated or tumor-specific antigen comprising the administration of a poxvirus expression vector comprising SEQ ID NO:1, or fragments of SEQ ID NO:1 encoding immunogenic fragments of the encoded protein.

The specification teaches that six clones were used in a BFA4 peptide-pulsed target experiment (page 35-36, bridging sentence). The specification provides 100 nonamer peptides selected for their "potential ability" to bind to HLA-A*0201 (Table V, pages 37-38). The specification states that pooled groups of the selected peptides were used to activate CTL which lysed target cells bearing the peptides (page 41, first paragraph). The specification teaches that single peptides from each group were tested to reveal a number of individual strongly reactive peptides recognized by human T cells and able to induce CTL activity in vitro (page 41, second paragraph). The specification is not enabling for administering the expression vectors to treat cancer by inducing a therapeutic immune response for the reasons set forth below nor is it enabling for a method of treating cancer comprising the administration of peptides derived from BFA4. Claims drawn to an expression vector which further incorporates tumor antigens, angiogenesis associated antigens or co-stimulatory molecules are included with the rejection as well as pharmaceutical composition because said products are clearly intended to be used for generating a therapeutic immune response to a BFA4 expressing cancer and the specification

does not teach how to use such an expression vector, encoding molecules important for the immune response .

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed expression vectors or viral vectors comprising the nucleic acids encoding BFA4. . The state of the art is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. The specification is not enabling for the selective targeting of an antigen-presenting cells effective to mount an immune response against a generic "cancer". and without teaching regarding how said construct is to be specifically targeted one of skill in the art would be subject to undue experimentation. Verma et al further state that an ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). The specification does not teach a dosage of plasmid or viral vector which could be used as an "efficient dose" in order to inhibit the solid tumors, nor does the specification disclose a method to obtain sustained expression of the BFa4 antigen. Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the sequence being expressed, and the disease being treated (Eck et al bridging pages 81-82). Thus, one of skill in the art would conclude that there is no nexus between the transfection of cell in vitro with constructs encoding BFA4 , and the successful modulation of the immune response against the BFA4 antigen sufficient to cause a therapeutic effect.

Using viral vectors to deliver anti-sense DNA to an organism in vivo is in the realm of gene therapy, and therefore highly unpredictable in view of the complexity of in vivo systems. Orkin states ("Report and Recommendation of the Panel to Assess the NIH Investment in

Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in these areas, slow and erratic success in applying gene transfer methods to patients can be expected".. Orkin teaches that adequate expression of the transferred genes is essential for therapy, but that data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. As stated above, the specification does not teach a vector having a specific regulatory sequence which would direct the expression of the BFA4 nucleic acids to the appropriate tissue and/or cell type.

It is noted that Ghose et al (Human Gene Therapy, 2000, Vol. 11, pp. 1289-1301) teach that mice receiving tumor cells infected with ALVAC viral vectors did not develop tumors versus control mice which were injected with tumor cells alone. However, it is well recognized in the art that clinical results on patients do not reflect the results of animal models. For example Schultze et al (Trends in Immunology, 2004, Vol. 25, pp 659-664) teach that encouraging animal model studies lead to clinical trails, but that the general outcomes of these trials are disappointing, citing a discrepancy between the outcome of pre-clinical models and the outcome of the human situation. Bodey et al, (Anticancer Research, 2000, Vol. 20, pp. 2665-2676) teach that the animal models often produce highly encouraging results but that the resulting response in humans is disappointing. Le Fur et al (PNAS, 1997, Vol. 94, pp. 7561-7565) teach that results pertaining to the rejection of transplanted tissue differs from raising an immune response in a patient against a primary tumor in its natural place (page 7564, second column, lines 13-15 in the third full paragraph). Le Fur et al conclude that many practical issues need to be resolved before an effective peptide-antigen tumor vaccine is obtained from peptides identified by T cell recognition or predicted by over expressed RNA isoforms in tumors (page 7565 last paragraph).

Donnelly et al (Journal of Immunology, 2005 Jul 15, 175(2):633-639 address the lack of nexus between the outcome of DNA vaccines in small mammals and humans, concluding (three years after the filing date of the instant application) that there is a disappointing potency of DNA vaccines in humans. This is corroborated by Vanniasinkam et al (Journal of Clinical Virology, 2006 Aug, 36(4):292-297) who state that ability to induce an effective immune response as a result of DNA vaccination in large animals and humans is disappointing.

The specification does not remedy any of the deficiencies or the prior art with regard to the administration of nucleic acids in vivo. Given the lack of any guidance from the specification on any of the above evidence of unreliability on the art, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the claimed methods.

(C)As drawn to the induction or enhancement of an immune response against a tumor-antigen

The prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4 and Finke et al, Immunology Today, 1999, Vol. 20, pp. 158-160, see page 159, under the heading "Barriers that prevent tumor recognition"). The specification has stated that certain of the disclosed peptides are able to activate CTL which lyse BFA4 expressing cells in vitro. Paul teaches that lymphocytes from tumor bearing patients have frequently been found to be cytotoxic to their own tumor cells in vitro, but that this effect was blocked by the addition of sera from said patients. Paul teaches that the constituent of the sera which caused the blocking of the cytotoxicity was unknown, but that antibodies, antibody-antigen complexes and shed antigen have all been implicated in the blocking phenomenon (Paul page 1167, second paragraph under the heading "Immunological Enhancement and Blocking Factors". Finke et al (ibid) teach that

tumor derived factors can alter T-cell function rendering tumor infiltrating lymphocytes dysfunctional (page 159, third column) and that an additional escape mechanism is stimulation of the Fas ligand by the tumor cells (page 159, third column). Finke et al teach that removal of the dysfunctional infiltrating lymphocytes from the tumor results in restoration of T-cell function directly implicating tumor, stoma or other host infiltrating cells on the repression of T-cell function (page 160 first column, lines 4-12). Paul also notes that in some cases, immune response to a tumor antigen may sometimes stimulate the growth of the tumor cells directly (last line under the heading "Immunological Enhancement and Blocking Factors", page 1167). With respect to the blocking factor found in serum, Apostolopoulos et al (Nature Medicine, 1998, vol. 4, pp. 315-320) teach that endogenous antibodies present at the time of administration of a tumor peptide re-routes the immune response from a cellular response to a humoral response. In preclinical experiments with mice, MUC1 peptides targeted to the mannose receptor produce high levels of CTL and a low level of antibodies. However, in human clinical trials a low level of CTL and a high level of humoral response was observed (Apostolopoulos, page 315, first column, bridging paragraph). Apostolopoulos et al teach that the presence of endogenous antibodies which bind to the MUC1 peptide was responsible for this re-routing of the immune response from cellular to humoral due to the Fc portion of the antibody (page 319, first column, lines 7-10). Apostolopoulos et al teach that mice are devoid of these antibodies (page 315, second column, lines 9-13) and are thus able to effectively mount a cellular immune response against the target antigen. Apostolopoulos et al teach that these findings have implication for other immunotherapy approaches (page 318, lines 4-8, under the heading "Discussion". In support of these conclusions Jager et al (PNAS, 2000, Vol. 97, pp. 12198-12203) teach that patients who do not have antibodies to the cancer testis antigen, NY-ESO-1, were able to generate a specific T-cell response to NY-ESO after intradermal administration, whereas patients having antibodies prior to treatment which reacted with said antigen already had T-cells which reacted with target cells expressing said antigen in vitro, and said positive patients did not develop significant CTL in response to the administered NY-ESO antigen. Finke et al (ibid) conclude that the immune dysfunction resulting from a progressively growing tumor is distinct from generalized immune suppression induced by pharmacological means and as such is not

understood (page 160 under the heading of "Conclusion"). These references serve to demonstrate that the induction of a anti-tumor CTL response after the administration of a tumor peptide is unpredictable.

Paul (ibid) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstract of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105) and the abstract of Algarra et al International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102) which all teach that primary tumors in situ are often heterogeneous with respect to MHC presentation. The effect of the claimed vaccine upon such a heterogeneous tumor has not been demonstrated by the specification. More currently, the abstract of Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teaches that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules.

Paul (ibid) states that the induction of tolerance is a mechanism by which tumor cells escape immune detection. The art recognizes that T-cell are subject to clonal deletion within the thymus of a host and that this mechanism eliminates T-cell which are reactive with self-antigens. Lauritzsen et al (International Journal of Cancer, 1998, Vol. 78, pp. 216-222) teach that clonal deletions of thymocytes is a major event in T-cell tolerance which could lead to a tumor escape mechanism. In transgenic mice homozygous for HLA-specific CD+4 T-cells which are specific for a MOPC315 plasmacytoma, injection of a large number of tumor cells results in apoptosis of immature and mature transgenic CD+4+8 and CD+4 thymocytes. This negative selection was specific for the transgenic thymocytes that would complement the idiotype of the immunoglobulins of the MOPC315 plasmacytoma, because injection of tumor cells from a plasmacytoma which had a different idiotype of immunoglobulins failed to elicit the clonal deletion. Lauritzsen et al teach that injection of purified MOPC315 protein, versus the tumor cells, caused a profound reduction of the specific thymocytes specific to the idiotype of the plasmacytoma. Lauritzsen et al conclude that deletion of tumor specific thymocytes may represent a major escape mechanism in patients with cancers that secrete of shed antigens. In the

instant case, the antigens are known self antigens. It would be reasonable to conclude that said normal antigens are presented within the thymus to developing thymocytes and T-cells with high affinity for said antigens are deleted as "self". It would be also reasonable to conclude that administration of the claimed polypeptides or cells expressing said polypeptides would not result in an efficacious vaccine as a T-cell response would not be evoked due to the process of clonal deletion in the thymus, rendering the host devoid of T-cells which are specific to the self-protein. Sarma et al (Journal of Experimental Medicine, 1999, Vol. 189, pp. 811-820) states that a critical issue in therapeutic regiments comprising the administration of tumor antigens for immunotherapy is whether un-mutated tumor antigens which are expressed in normal cells impose special restrictions on the CTL response in vivo. Using transgenic mice wherein the antigen specific T cells specific for the P1A non-mutated tumor antigen are expressed at high levels and remain responsive to the P1A antigen when assayed in vitro, it was found that P1A antigen expressed in the thymus resulted in clonal deletion of said specific T-cells Sarma et al note that although said transgenic mice produce an overwhelming majority of T cells that are specific for P1A, said mice are no more resistant to cells expressing P1A than non-transgenic litter mates. Sarma et al concludes that even thought P1A can be a tumor rejection antigen, the effector function of P1A specific CTL is restrained in vivo and that these results have important implications for the strategy of tumor immunotherapy. Further, the presence of CTL which can lyse target cells in vitro has no apparent nexus with anti-tumor cytolytic activity in vivo. Ohlen et al (Journal of Immunology, 2001, Vol.166, pp. 2863-2870) teach that T-cells recognizing normal proteins expressed in tumors can be isolated in vitro, but that the existence of said T-cells does not preclude in vivo anergy induction and deletion (page 2863, second column, lines 1-6 of the last paragraph). Antoinia et al (International Immunology, 1995, Vol. 7, pp. 715-725) teach that T-cells which are impaired in the ability to proliferate in response to antigen and unable to reject tumors in vivo were fully functional as CTL lymphocytes in vivo (page 724, first column, first full paragraph). Yu and Restifo (Journal of Clinical Investigation, 2002, Vol. 110, pp. 289-294, especially page 292) teach that even when increased anti-tumor T-cell precursors have been induced by vaccination, the clinical response is partial and transient and most patients eventually succumb to progressively growing tumors. Further, Lee et al (Journal of Immunology, 1999,

vol. 163, pp. 6292-6300) corroborate these findings, stating that although peptide based vaccines can effectively generate a T-cell specific response in the PBMC of cancer patients, said response is not associated with a clinically evidence regression of metastatic melanoma (page 6297, under the heading of "enhancement of vaccine-specific T cell..."). These references serve to demonstrate that induction of a CTL by means of the administered antigens of the invention or the demonstration that said CTL can lyse target cells expressing a tumor associated-antigen in vitro does not constitute evidence that T-lymphocytes would be effective at lysing tumor cells in vivo.

It is noted that the types and stages of generic cancers encompassed by the claims would not be expected to initiate or maintain the same growth kinetics. This is of importance with regard to the teachings of Paul (ibid) on tumor cell escape mechanisms which include rapid growth as a means to overwhelm a slower immune response, (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4) and deficient antigen processing by tumor cells . With regard to the antigen processing, it is unclear whether all patients having a tumor associated antigen would have peripheral T-cells which were specific from the disclosed antigen, as the art teaches that the presence of a small number of tumor cells or the presence of a large number of tumor cells gives rise to tolerance (Paul, page 1166, second column, lines 19-23 under the heading "Sneaking Through"). Based on this observation, it is reasonable to conclude that a small number of slow growing tumor cells would elicit tolerance, and a large number of rapidly growing tumor cells would also elicit tolerance in line with the bi-phasic response reported by Paul. Thus, it appears that the interaction of the tumor cells with the host can produce tolerance by means of clonal deletion within the thymus of said host.

Further, claim 37 is drawn to the administration of any of the peptides in Tables V, VI or VII. It is clear from the specification, that not all of the predicted peptides have the ability to activate CTL against BFA4 expressing target cells because the specification teaches the pooling of the peptides and the deconvolution of the pooled peptides into a few individual peptides responsible for the activity in vitro (page 41, first and second paragraphs). Further the art teaches that "putative epitopes" can be predicted using a computer to scan the sequence of the

gene (antigen) for amino acid sequences that contain a "motif" or a defined pattern of amino acid residues associated with a particular MHC (HLA) allele, but that upon testing in standard functional assays, the vast majority of these "predicted" epitopes failed to be immunogenic (Burch WO 03/084467 Oct 16, 2004). The specification fails to address how to use peptides which were not able to induce a CTL response against BFA4. Further, claims 31-35 are reliant in part on nucleic acids encoding a fragment of SEQ ID NO:25 and 27. It is noted that these SEQ ID NO are nine-mer peptides. The specification provides no guidance for the selection of smaller fragments of SEQ ID NO:25 or 27 sufficient to treat cancer when expressed via an expression vector.

Given the lack of guidance for all the above issues and the unreliability of treating cancer by the induction of a CTL response targeting said cancer, one of skill in the art would be forced into undue experimentation in order to use the claimed products or carry our the claimed methods for the treatment of cancer.

In a recent article published in 2006,Young et al (Journal of Pathology, 2006, Vol. 208, pp. 299-318) teach that

"transient gene delivery in the context of major contemporary diseases such as cancer and heart disease may be more likely to offer significant clinical benefit within the next decade".

Thus, it can be concluded that the instant invention would require undue experimentation because as of 2006, four years after the earliest effective filing date claimed,, the art is still immature for how to elicit a clinical benefit from transient gene delivery and predicts that clinical efficacy can be attained within another decade.

(B)As drawn to the NYVAC, ALVAC, ALVAC(2) and TROVAC expression vectors

Claims 4, 5, 9, 10, 14, 15, 19, 20, 24, 25, 29, 30, 34, 35, 47, 48, 52, 53, 57, 58, 62 and 63 require the NYVAC, ALVAC(2), ALVAC and/or TROVAC vector. The specification states that NYVAC, ALVAC and TROVAC were deposited under the terms of the Budapest Treaty (pages 23-24). It is unclear whether one of skill in the art could make the identical vectors of NTVAC, ALVAC and TROVAC without undue experimentation. Therefore the deposit for patent purposes is required in order to satisfy the requirements of 112, first paragraph. However, applicant's referral to the deposits on pages 23-24 of the specification is s an insufficient

assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 have been met.

If the deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposits have been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposits will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CRF 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his/her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological materials will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced should they become non-viable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record,

applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited biological materials are producing the NYVAC, ALVAC and TROVAC vectors as described in the specification as filed and are the same as those deposited in the depository, stating that the deposited materials are producing identical vectors as NYVAC, ALVAC and TROVAC as described in the specification and were in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

Applicant argues that it is the property of being unable to sustain replication in mammalian cells that makes the instant expression vectors enabled for the practice of the method claims. this has been considered but not found persuasive. This statement about the property of the expression vectors was used by the examiner to discount the usage of expression vectors in a well-known and ordinary manner to induce the expression of the expressed protein in mammalian cells. Applicant argues that sustained expression and/or targeted expression is not critical for the instant invention which requires only the induction of an immune response. Applicant asserts that at least some of the immunogenic fragment disclosed in the specification are able to stimulate T cell responses that would enable one of skill in the art that would be expected to have a therapeutic effect. This has been considered but not found persuasive. As stated above, Young et al (Journal of Pathology, 2006, vol. 208, pp. 299-318) teach that

"transient gene delivery in the context of major contemporary diseases such as cancer and heart disease may be more likely to offer significant clinical benefit within the next decade".

Thus, it can be concluded that the instant invention would require undue experimentation because as of 2006, four years after the earliest effective filing date claimed,, the art is still immature for how to elicit a clinical benefit from transient gene delivery and predicts that clinical efficacy can be attained within another decade.

Applicant states the intention of complying with the deposit requirement.

All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants amendments.

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A. Canella/
Ph.D., Primary Examiner
ArtUnit 1643